DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed August 20, 2007 is acknowledged. Claims 1-25, 27-34, 38, 39, 44-56, and 62 are cancelled. Claims 26, 40, 41, 43, 57 and 60 are amended. Claim 64 is newly added. Claims 26, 35-37,40-43, 58-61, 63 and newly added claim 64 are pending in this application. Claim 37 is withdrawn with traverse (filed on 1/12/06) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/12/06.

2. Claims 26, 35, 36, 40-43, 57-61, 63 and 64 are under examination with respect to Aβ (4-42) and Aβ (5-42) in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

4. Applicant's arguments filed on August 20, 2007 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Maintained

In view of the amendment filed on 8/20/07, the following rejections are maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 35, 36, 40-43, 57-61, 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is maintained for the reasons made of record in the office action mailed on 5/15/07, and as follows.

At p. 8-10 of the response, Applicant argues the claimed invention is enabled because claim 26 has been amended to address the discussion during the interview with the examiners. Applicant argues that claim 26 is enabled because it has been amended to limit Aβ variants to Aβ (2-42), (3-42), (4-42), (5-42), (6-42), (7-42), (8-42) and (9-42) that are positively correlates with detection of a disease associated with β-amyloid formation/aggregation. Applicant argues that detection of Ab8-42 in one of the controls listed in tables 6 and 8 was a false negative control due to mislabeling a patient suffering from pathological change without AD symptoms. Applicant submits a supplemental declaration of Dr. in support of the argument. Applicant's arguments have been fully considered but they are not persuasive.

The declaration and the supplemental declaration under 37 CFR 1.132 filed on 2/23/07 and 8/20/07 respectively are insufficient to overcome the rejection of claims 26, 35, 36, 40-43, 57-61, 63 and 64 based upon the insufficiency of disclosure under 112 first paragraph, lack of enablement, as set forth in the last Office action because: the

showing and the cited reference (Braak et al. Clin. Neurosci. 1999. 249: 14-22) do not support for the enablement of the claimed invention.

In response, based on the declaration (i.e. table 8 and Appendix 3 table 1), although the detection of Aβ8-42 is a false negative control, Aβ8-42 and Aβ4-42 also can be detected in most of control patients and patients with MCI, dementia or AD (Appendix 3 table 1). In addition, Aβ8-42 and Aβ5-42 cannot be detected in patients with DLB (dementia with Lewy body) and cogn (cognitive impairment without development of AD). Aβ5-42 cannot be detected in two thirds of patients with MCI-AD (mild cognitive impairment-later developed AD) and mild AD (i.e. based on two samples out of three patients are negative) and one third of patients with moderate AD. Aβ8-42 cannot be detected in one third of patients with MCI-AD and mild-AD. Further, Aβ8-42 is high in S0, but all variants cannot be detected in Appendix 3 table 1. These data indicate that the expression of the different Aβ variants varies in different patients with different status, which is no specific standard, suggesting that the claimed method is not specific or sensitive to evaluate or determine whether a person is susceptible to or at risk of a disease associated with β-amyloid formation and aggregation. A skilled artisan cannot practice the claimed invention based on the disclosure alone.

Based on the specification, Applicant is enabled for detecting Aβ2-42, Aβ3-42, Aβ4-42, Aβ5-42, Aβ6-42, Aβ7-42 and Aβ8-42 variants or the variants with post-translation modification in CSF of patients suffering from AD (i.e.patients have been diagnosed with a specific AD or amyloid-associated disorders) and S0 controls or other controls. Based on the data derived from detection of different Aβ variants in controls

and in patients who have been diagnosed with different amyloid associated diseases, Applicant extrapolates the data to the claimed method. However, Applicant is not enabled for a method for aiding in the determination of whether a patient is susceptible to or at risk of a disease associated with β-amyloid formation and/or aggregation without specific knowledge of the expression profile of specific variants that are present in patients known not to suffer from the disease. Applicant is not enabled for the claimed method to predict and determine whether a person is susceptible or at risk to a disease associated with amyloid formation or aggregation because the detection of different Aβ variants in different status of patients could be false positive or false negative, in particular Aβ8-42 or Aβ4-42 or Aβ5-42 as discussed above and as shown in the specification and as evidenced by Applicant's declaration. In addition, Applicant fails to provide a standard expression profile of Aβ variants in controls known not to suffer from a disease associated with β-amyloid formation and/or aggregation. It is unpredictable what expression levels and what specific species of Aβ variants can be measured and used to determine whether a person is susceptible to or at risk of the disease.

Note that

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03

In addition, a patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that: "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution. Thus, the rejection of claims 26, 35, 36, 40-43, 57-61, 63 and 64 under 35 U.S.C. §112, first paragraph, because the specification does not enable the invention commensurate in scope with the claim is maintained.

New Grounds of Rejection Necessitated by the Amendment

The following rejections are new grounds of rejections necessitated by the amendment filed on 8/20/07.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

There are two separate requirements set forth in this paragraph: (A) the claims must set forth the subject matter that applicants regard as their invention; and (B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

Claims 26, 35, 36, 40-43, 57-61, 63 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26, 35, 36, 40-43, 57-61, 63 and 64 are indefinite because Applicant recites greater and typically in claim 26. The rest of claims are indefinite as depending from an indefinite claim. The term "greater" and the term "typically" in claim 26 are a relative term, which renders the claims indefinite. The terms "greater" and "typically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant fails to set for the metes and bounds of what is encompassed within the definition of "greater" and "typically". Since the metes and bounds are not unknown, a skilled artisan cannot determine what amount of the expression of Ab variants and what specific Ab variants would be in controls vs. in patients susceptible to or at risk of a disease associated with amyloid formation and aggregation as recited in the claim. Thus these claims are indefinite.

Conclusion

7. NO CLAIM IS ALLOWED.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should

applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
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October 30, 2007

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